23. Cancelled.

24. Cancelled.

25. Cancelled.

26. (Amended) Use of a pharmaceutical composition comprising $sPLA_2$ inhibitor compounds according to Claim 1 and mixtures thereof for [the manufacture of a medicament for the therapeutic]treatment of Inflammatory Diseases comprising administering a therapeutic amount of said compound to a patient in need thereof.

Remarks

In the application, Claims 1-26 inclusive are pending. Applicants, pursuant to Examiner's restriction requirement, elected without traverse, the claims encompassed by Group I as restricted by the Examiner. Examiner subsequently offered a rejection dated August 25, 2002, which is the basis for this response.

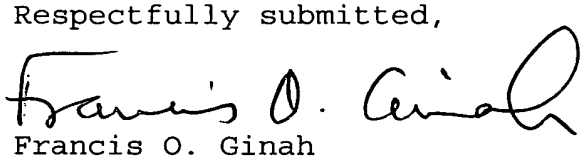
Applicants herewith, amend Claims 1-13 to remove non-elected species. Applicants have also amended or cancelled Claims 14, 16, 17, 19, 20 and 23-26. In the originally filed PCT application, two Claim 20's were listed. We are canceling both of these claims. Applicants reserve the right to reintroduce some of these claims as appropriate, particularly in a division application.

Consequently, Applicants have enclosed a clean version and a marked-up version of the original claims.

Applicants believe that no new matter has been added by

the amendments herein, and that the claims should now be in condition for allowance.

Respectfully submitted,



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Phone: 317-276-9477

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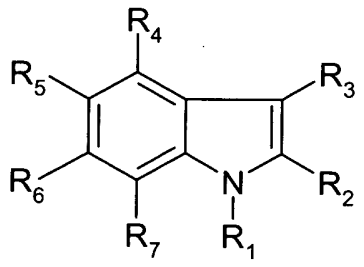
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

September 24, 2002

Marked Up Version of Claims (9/20/02)

WE CLAIM:

1. An indole compound represented by the formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof;



(I)

wherein ;

R_1 is selected from groups (a), (b), and (c) wherein;

(a) is C_7-C_{20} alkyl, C_7-C_{20} haloalkyl, C_7-C_{20} alkenyl, C_7-C_{20} alkynyl[,]or carbocyclic radical, or [heterocyclic radical, or]

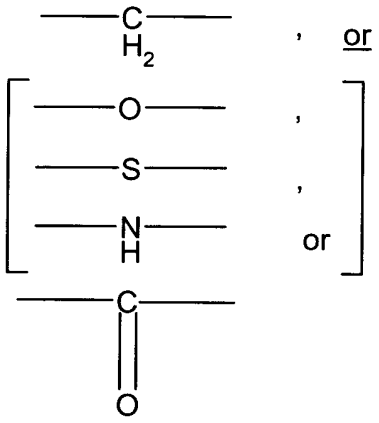
(b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a)

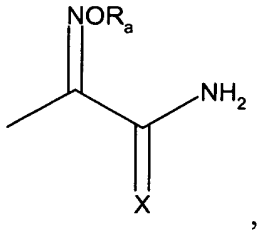
or (b);

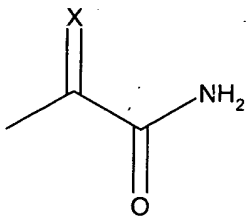
R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

R_3 is $-(L_3)-$ Z, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:

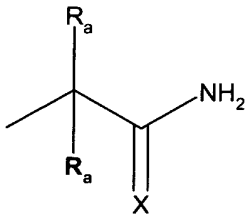


and Z is selected from a group represented by the formulae,





or



wherein, X is oxygen [or sulfur;]and R_a is selected from hydrogen, C_1-C_8 alkyl, aryl, C_1-C_8 alkaryl, C_1-C_8 alkoxy, aralkyl and -CN;

R_4 is the group, -(L_C)-(acylamino acid group); wherein -(L_C)-, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

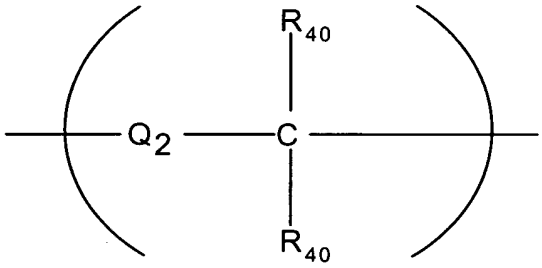
R_5 is selected from hydrogen[,]or a non-interfering substituent[, or the group, -(L_a)-(acidic group); wherein -(L_a)-, is an acid linker having an acid linker length of 1 to 8];

R_6 and R_7 are selected from hydrogen[,]or a non-interfering substituent[, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s),

heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s)].

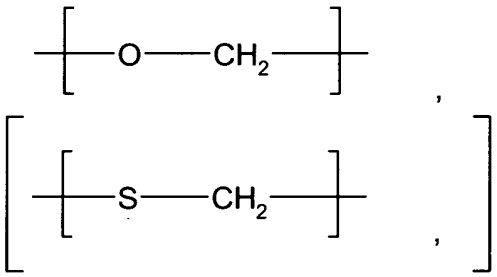
2. The compound of claim 1 wherein R_2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, -O-(C_1-C_3 alkyl), -S-(C_1-C_3 alkyl), C_3-C_4 cycloalkyl, $-CF_3$, halo, $-NO_2$, -CN, or $-SO_3$.

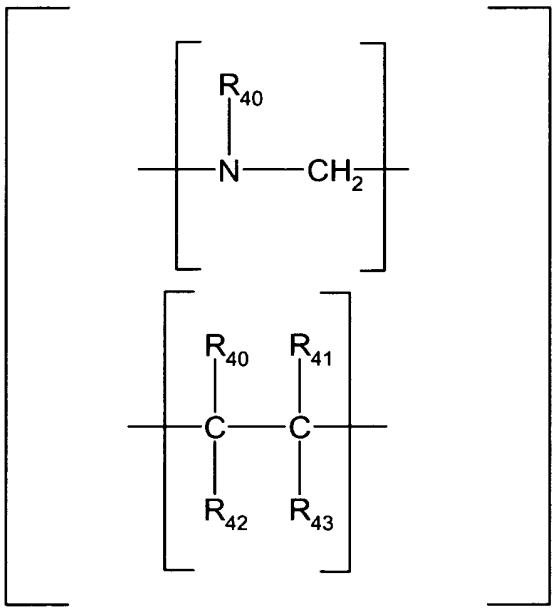
[3. The compound of Claim 1 wherein the acylamino acid linker group, -(L_C)-, for R_4 is selected from a group represented by the formula;

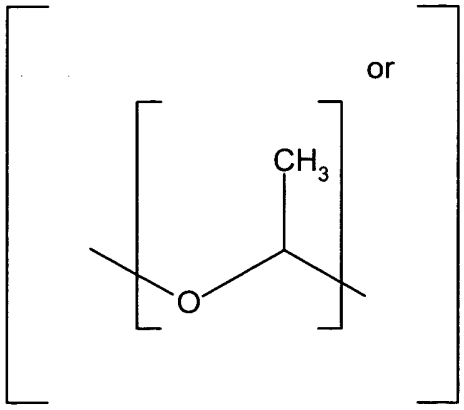


where Q_2 is selected from the group -(CH_2)-, -O-, -NH-, -C(O)-, and -S-, and each R_{40} is independently selected from hydrogen, C_1-C_8 alkyl, aryl, C_1-C_8 alkaryl, C_1-C_8 alkoxy, aralkyl, and halo.]

4. The compound of Claim 1 wherein the acylamino acid linker group, -(Lc)-, for R_4 [selected from -(L_C)-] is a divalent group selected from,

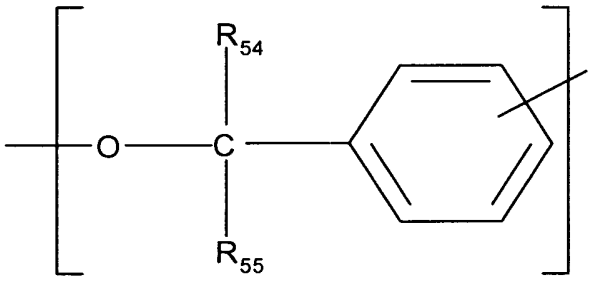






[where R_{40}, R_{41}, R_{42}, and R_{43} are each independently selected from hydrogen, C_1-C_8 alkyl.]

[5. The compound of Claim 1 wherein the acid linker, -(L_a)-, for R_5 is selected from a group represented by the formulae consisting of;



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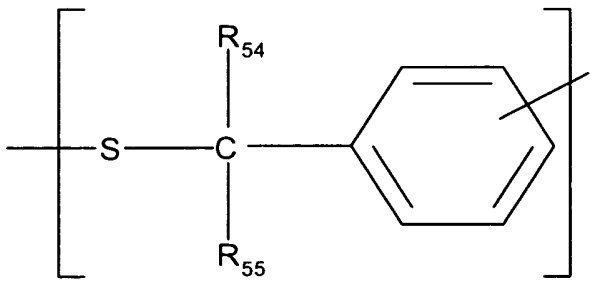

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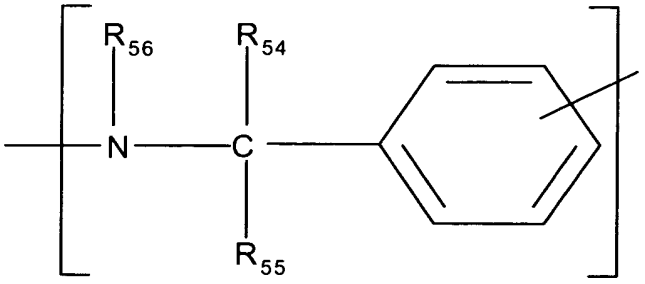
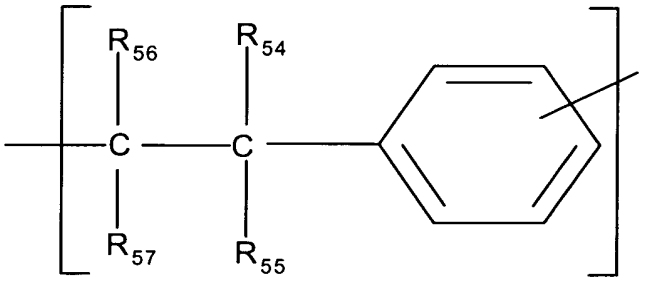
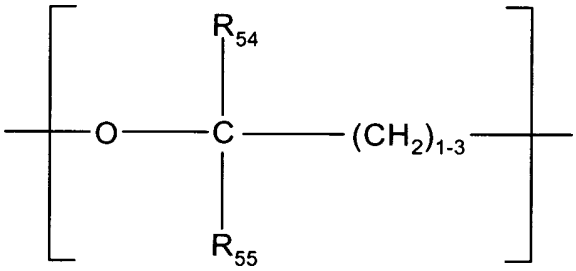

R56
R54
N
C
R55

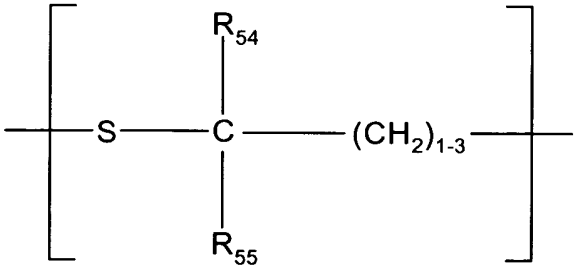
,


R56
R54
C
C
R57
R55

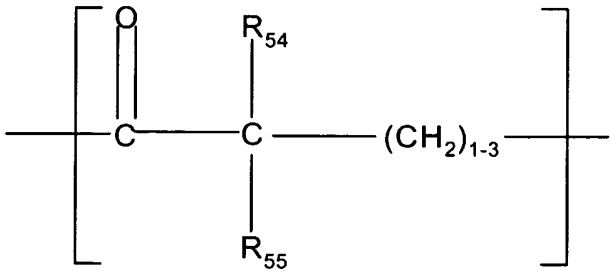
,


R54
O
C
(CH2)1-3
R55

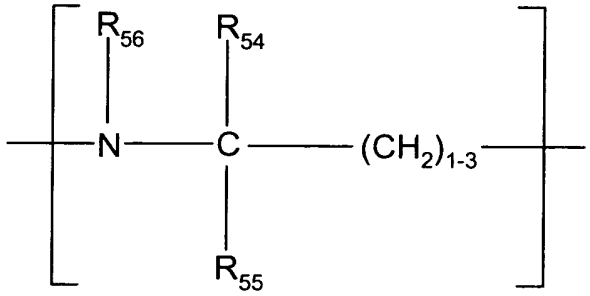
,


R54
S
C
(CH2)1-3
R55

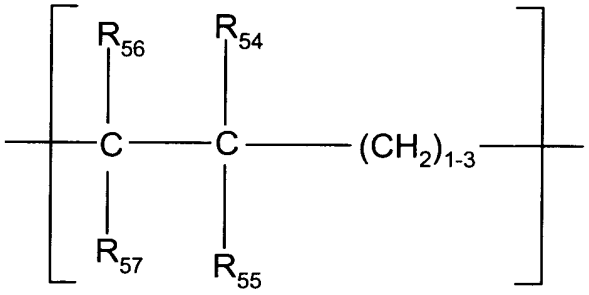
,


O
R54
C
C
(CH2)1-3
R55

,



and



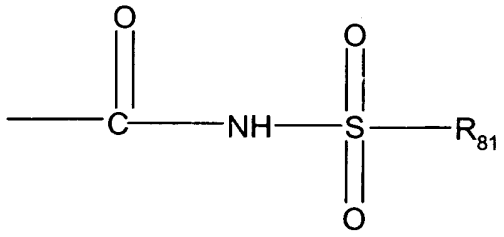
;

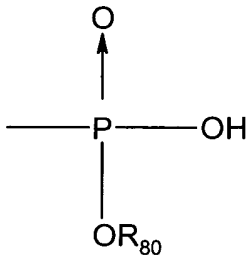
wherein R_{54}, R_{55}, R_{56} and R_{57} are each independently hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, aryl, C_1-C_8 alkoxy, or halo.]

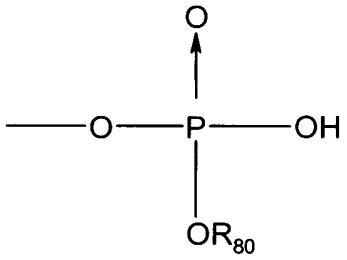
[6. The compound of claim 1 wherein R_5 is the group, -(L_a)-(acidic group) and wherein the (acidic group) is selected from the group:

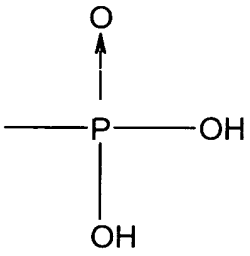
-5-tetrazolyl,

-SO_3H,

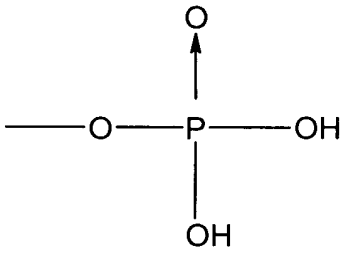

O
O
C
NH
S
R_{81}
O


O
P
OH
OR_{80}

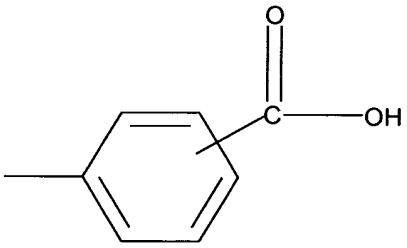

O
O
P
OH
OR_{80}



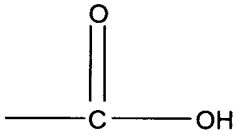
,



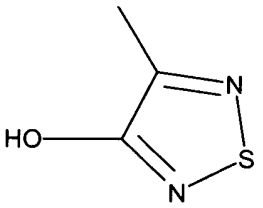
,



,

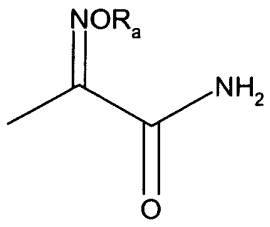


or



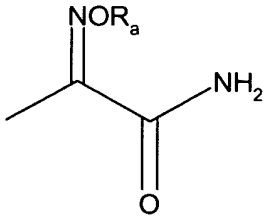
where R_{80} is a metal or C_1-C_8 alkyl and R_{81} is an organic substituent or $-CF_3$.]

7. The compound of claim 1 wherein for R_3, Z is the group represented by the formula;



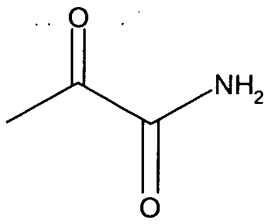
and the linking group -(L_3)- is a bond; and R_a is hydrogen, methyl, ethyl, propyl, isopropyl, phenyl or benzyl.

8. The compound of claim 1 wherein for R_3, Z is the group represented by the formula;



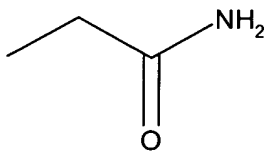
and the linking group -(L_3)- is a bond; and R_a is hydrogen.

9. The compound of claim 1 wherein for R_3, Z is the group represented by the formula;



and the linking group -(L_3)- is a bond.

10. The compound of claim 1 wherein for R_3, Z is the group represented by the formula;

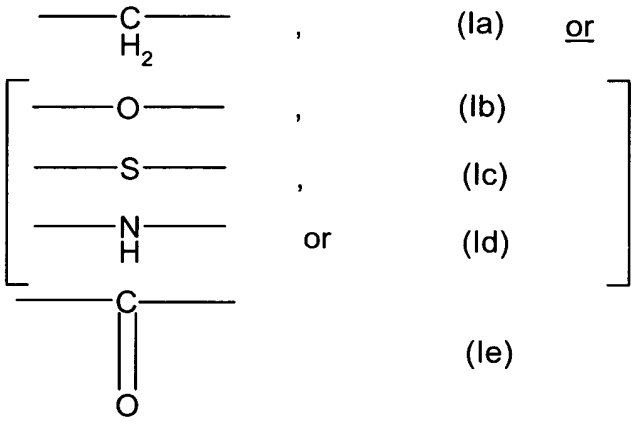


and the linking group -(L_3)- is a bond.

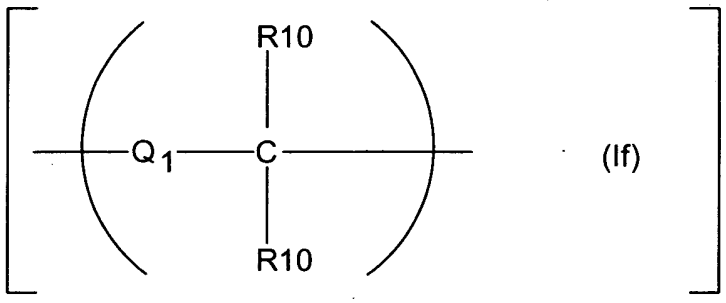
11. The compound of Claim 1 wherein, for R_6 the non-interfering substituent is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_8 alkoxy, C_2-C_8 alkenyloxy, C_2-C_8 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_1-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_8 alkylsulfinyl, C_1-C_8 alkylsulfonyl, C_2-C_8 haloalkoxy, C_1-C_8 haloalkylsulfonyl, C_2-C_8 haloalkyl,

C_1-C_8 hydroxyalkyl, -C(O)O(C_1-C_8 alkyl), -$(CH_2)_n$-O-(C_1-C_8 alkyl), benzyloxy, phenoxy, phenylthio, -($CONHSO_2R$), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -$(CH_2)_n$-CO_2H, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO_3H, thioacetal, thiocarbonyl, or carbonyl; where n is from 1 to 8.

12. The compound of Claim 1 wherein for R_1 the divalent linking group -(L_1)- is selected from a group represented by the formulae (Ia), (Ib), (Ic), (Id), (Ie), and (If):



[or]

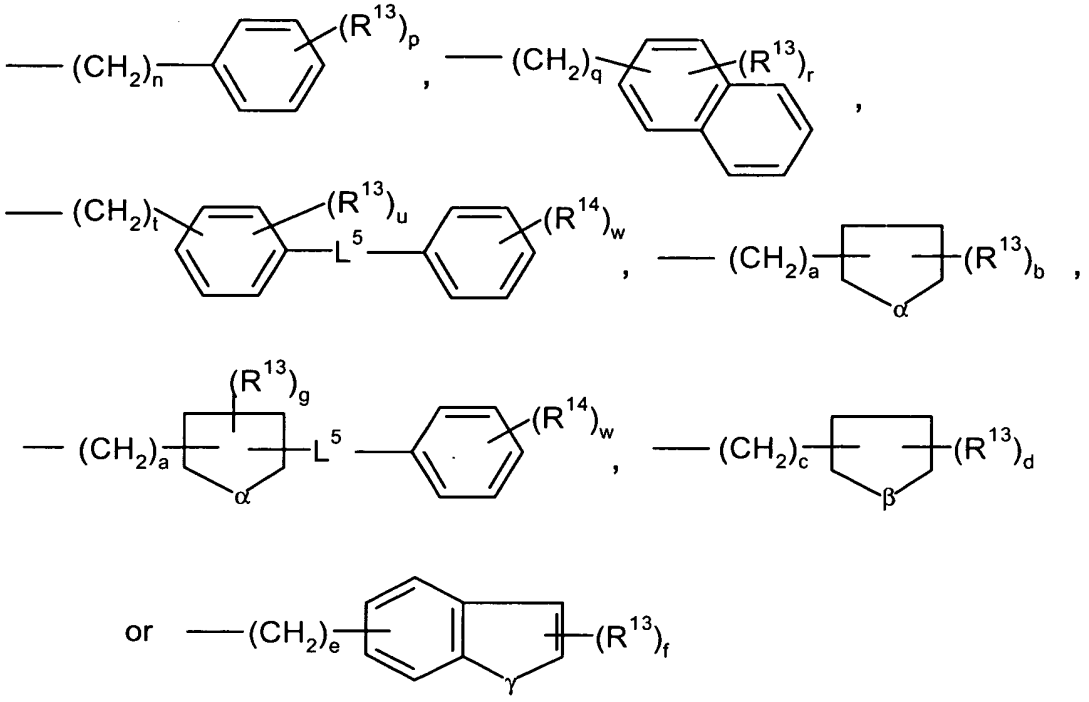


(If)

[where Q_1 is a bond or any of the divalent groups Ia, Ib, Ic, Id, and Ie and R_{10} is independently -H, C_{1-8} alkyl, C_{1-8} haloalkyl or C_{1-8} alkoxy.]

13. The compound of claim 1 wherein the linking group $-(L_1)-$ of R_1 is $-(CH_2)-$[or $-(CH_2-CH_2)-$].

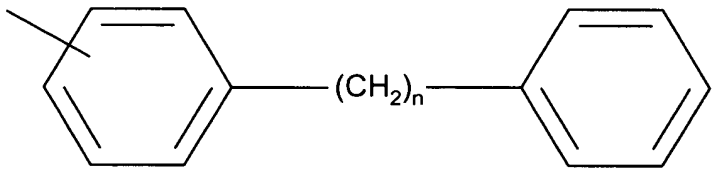
[14. The compound of claim 1 wherein the linking group $-(L_{11})-$ of R_{11} is a bond and R_{11} is $-(CH_2)m-R^{12}$ wherein m is an integer from 1 to 6, and R^{12} is a group represented by the formula:



wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)v-$, -C=C-, -CC-, -O-, or -S-, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C_1 to C_6

alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 haloalkyloxy, C_1 to C_8 haloalkyl, aryl, and a halogen..]

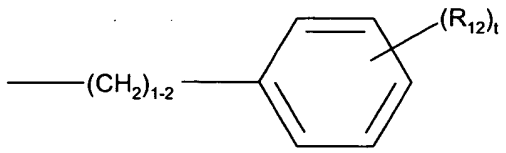
15. The compound of claim 1 wherein for R_1 the group R_{11} is a substituted or unsubstituted carbocyclic radical selected from the group consisting of cycloalkyl, cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a):



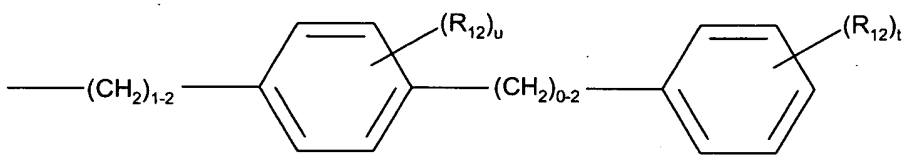
(a)

where n is a number from 1 to 8.

[16. The compound of Claim 12 wherein for R_1 the combined group $-(L_1)-R_{11}$ is selected from the groups;



or

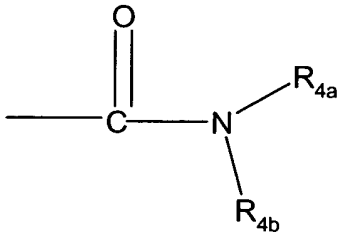


where R_{12} is a radical independently selected from halo, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, -S-(C_1-C_{10} alkyl), and C_1-C_{10} haloalkyl, C_1-C_{10} hydroxyalkyl and t is a number from 0 to 5 and u is a number from 0 to 4.]

[17. The compound of claim 1 wherein for R_1 the radical R_{11} is a substituted or unsubstituted heterocyclic radical selected from pyrrolyl, pyrrolodinyl, piperidinyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl, dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1.2-A)pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl, dipyridylyl. phenylpyridinyl, benzylpyridinyl,

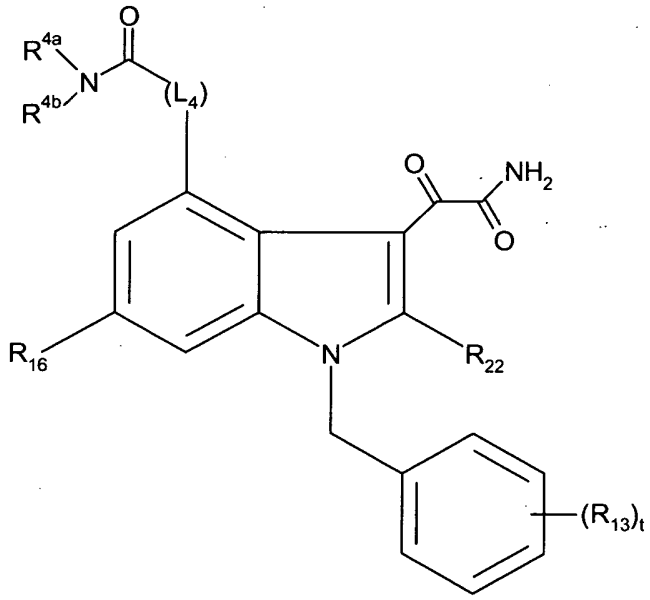
pyrimidinyl, phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl, quinazolinyl-morpholino, thiomorpholino, homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl, oxacanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, tetrahydrothiopheneyl, pentamethylenesulfadyl, 1,3-dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidinyl, hexamethyleneiminium, heptamethyleneiminium, piperazinyl or quinoxalinyl.]

18. The compound of claim 1 wherein R_4 is the group, -(L_C)-(acylamino acid group) and wherein the (acylamino acid group) is:



and R^{4a} is selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, heteroaryl and aryl; and wherein NR^{4b} is an amino acid residue with the nitrogen atom being part of the amino group of the amino acid.

[19. An indole compound represented by the formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof;



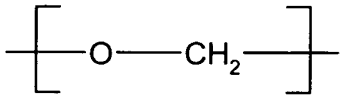
(II)

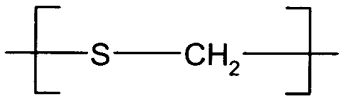
wherein ;

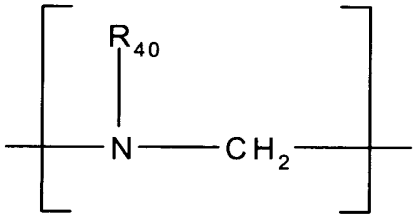
R_{22} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, $-CF_3$, -Cl, -Br, or $-O-CH_3$;

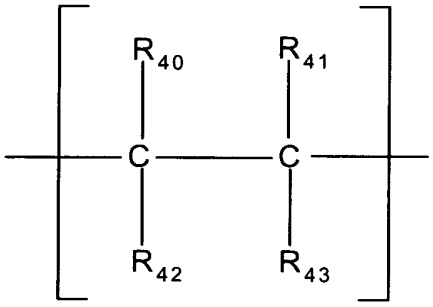
R^{4a} is hydrogen; and

NR^{4b} is an amino acid residue with the nitrogen atom being part of the amino group of the amino acid, and $-(L_C)-$ is a divalent group selected from;

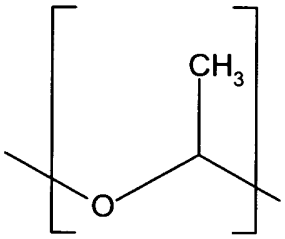








or

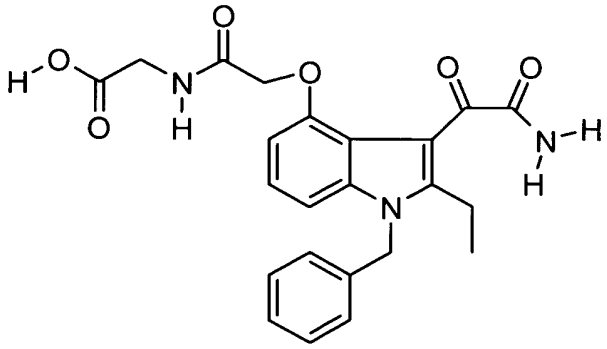


where R_{40}, R_{41}, R_{42}, and R_{43} are each independently selected from hydrogen or C_1-C_8 alkyl.

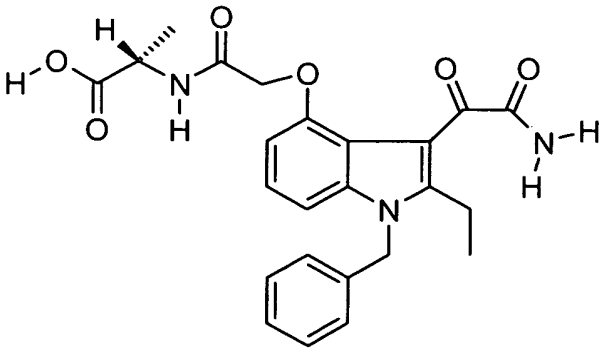
R_{16} is selected from hydrogen, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, and halo.

R_{13} is selected from hydrogen and C_1-C_8 alkyl, C_1-C_8 alkoxy, -S-(C_1-C_8 alkyl), C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, phenyl, halophenyl, and halo, and t is an integer from 0 to 5.]

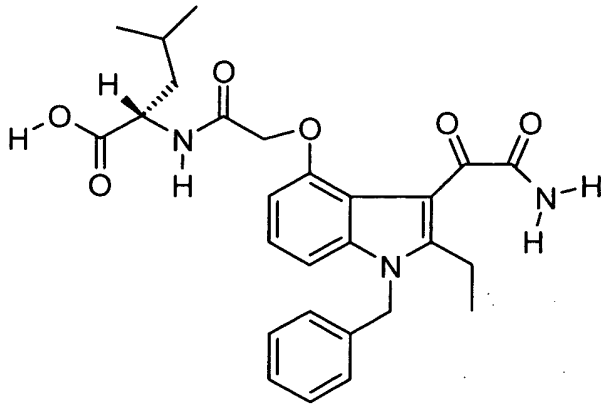
[20. An indole compound represented by the formulae (C1), (C2), (C3), (C4), (C5), (C6), (C7), (C8), (C9), (C10) or (C11);



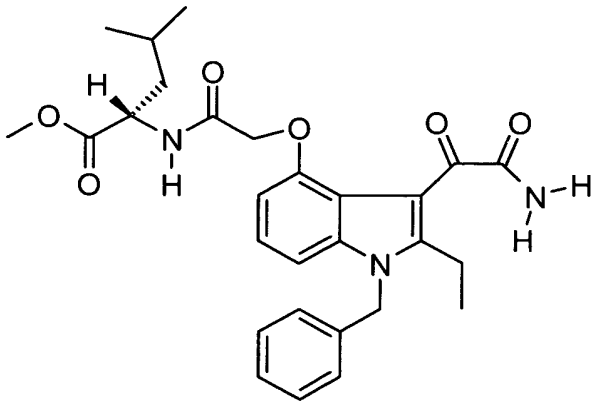
(C1),



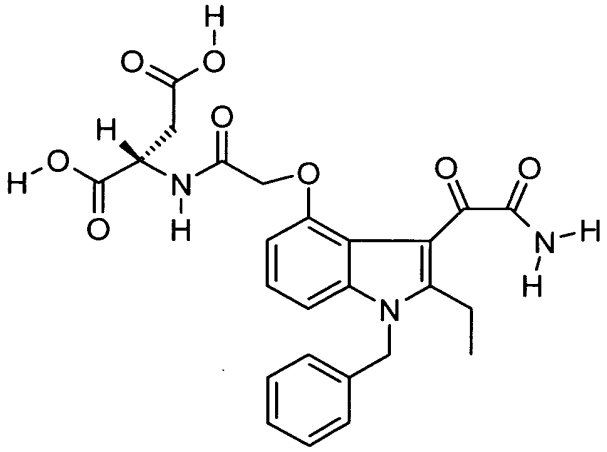
(C2),



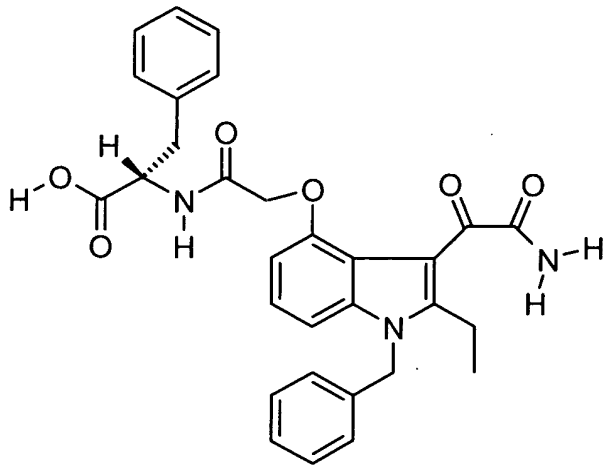
(C3),



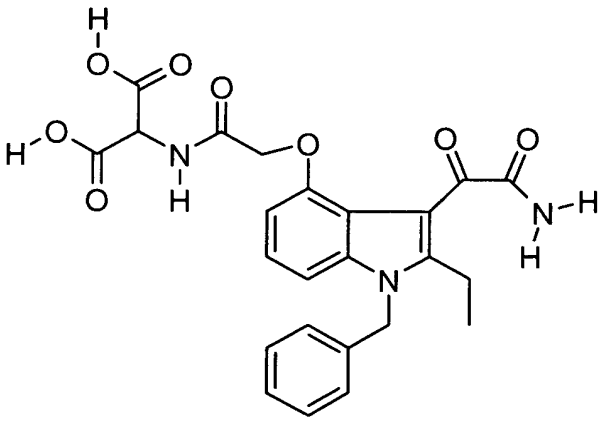
(C4),



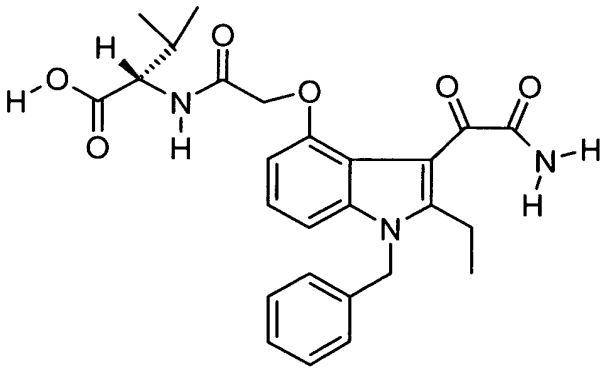
(C5),



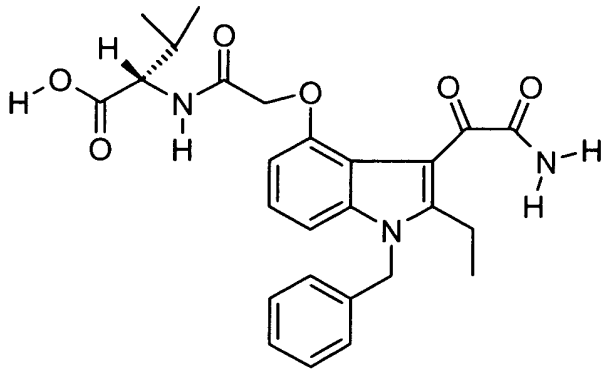
(C6),



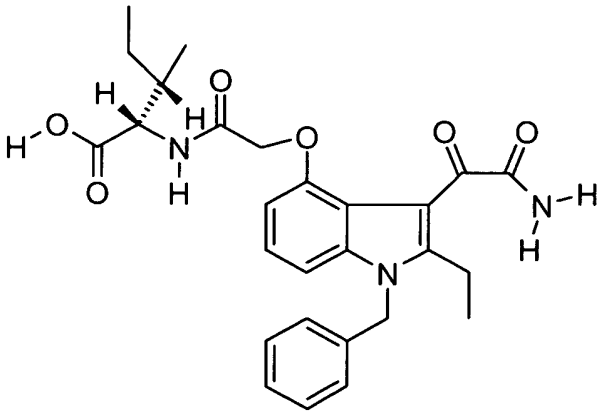
(C7),



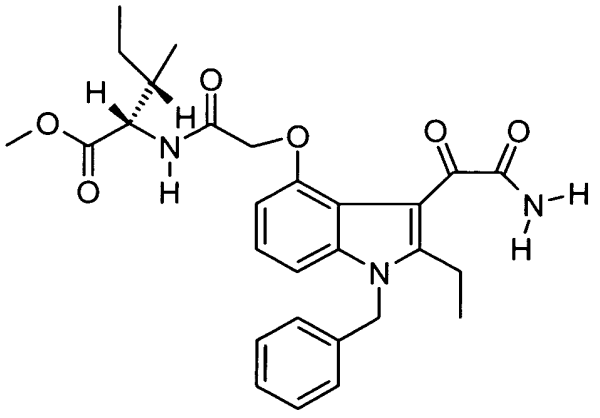
(C8),



(C9),



(C10) and



(C11)

or pharmaceutically acceptable salts or prodrugs thereof.]

[20. A compound of claim 1 selected from the group consisiting of:

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine.]

21. A pharmaceutical formulation comprising a indole compound as claimed in claim 1 together with a pharmaceutically acceptable carrier or diluent therefor.

22. A method of inhibiting $sPLA_2$ mediated release of fatty acid which comprises contacting $sPLA_2$ with a therapeutically effective amount of indole compound as claimed in claim 1.

[23. A method of treating a mammal, including a human, to alleviate the pathological effects of Inflammatory Diseases; wherein the method comprises administration to said mammal of at least one indole compound as claimed in Claim 1 in a pharmaceutically effective amount.]

[24. A compound of claim 1 or a pharmaceutical formulation containing an effective amount of the compound of claim 1 in treatment of Inflammatory Diseases.]

[25. A compound of claim 1 or a pharmaceutical formulation containing an effective amount of the compound of claim 1 for use as an inhibitor for inhibiting $sPLA_2$ mediated release of fatty acid.]

26. Use of a pharmaceutical composition comprising $sPLA_2$ inhibitor compounds according to Claim 1 and mixtures thereof for [the manufacture of a medicament for the therapeutic]treatment of Inflammatory Diseases comprising administering a therapeutic amount of said compound to a patient in need thereof.